Clinical Studies for Local Delivery of Nasal Aerosols and Sprays

Izabela J. Roman, MD, PhD Founder & Medical Director Target Research Associates, Inc.

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Bioequivalence is assumed when the 90% confidence interval ranges between 80 - 120% for the target parameters (for normally distributed data).

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Three Clinical Models

- Day(s) in the Park
- Environmental Unit
- Traditional Clinical Study

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Model 1 continued DAY(S) IN THE PARK STUDY

Strengths

- Short duration implications for less variability
- Cohort enrollment less environmental variability
- More controlled compliance
- Potential for greater number of time points for subjective and objective data

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Model 1 continued DAY(S) IN THE PARK STUDY

Weaknesses

- · Restricted to seasons
- Short duration drug may not reach max effect
- Weather risk
- Lack of site/population diversity less representative of geography of the entire U.S.
- Susceptible to single investigator influence
- · Lower variability than traditional study model
- Potential for high incidence of some AE's, e.g. sedation, since subjects often bored
- Not good for safety over time information

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Model 1 continued DAY(S) IN THE PARK STUDY

Most Frequently Used for:

- Pilot efficacy of new drugs
- · Onset of action
- Dose response
- Duration of effect for single dose

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Model 1 continued DAY(S) IN THE PARK STUDY

Bioequivalence Potential

Low for drugs that take >2 days to reach maximum effect

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Model 1 continued DAY(S) IN THE PARK STUDY

Cost

- Up to 50 to 100 patients per treatment group
- Approx. \$2,000 per patient investigator grant

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Model 2 continued ENVIRONMENTAL UNIT

Strengths

- Same as for Day(s) in the Park model
- Controlled environment no environmental variability
- All year round not seasonal
- Good model for non-seasonal allergens (e.g. cat)

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Model 2 continued ENVIRONMENTAL UNIT

Weaknesses

- Farthest from reality
- Limited number of centers available
- Short duration drug may not reach max effect
- Complex protocol priming & establishing baseline
- Very short observation period; relevant only for a single dose study
- · Safety information limited

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Model 2 continued ENVIRONMENTAL UNIT

Most Frequently Used for:

- Onset of action
- Pilot efficacy
- Single-dose studies

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Model 2 continued ENVIRONMENTAL UNIT

Bioequivalence Potential LOW

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Model 2 continued ENVIRONMENTAL UNIT

Cost

- 30 patients per treatment group
- \$5,000 per patient investigator grant

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Model 3 continued TRADITIONAL CLINICAL STUDY

Strengths

- Closest to reality
- Availability of sites
- · Well tested and validated
- Geographic diversification
- Longer duration versus other models implications regarding steady state efficacy as well as longer term safety.

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Model 3 continued: TRADITIONAL CLINICAL STUDY

Weaknesses

- High variability across sites
- Greater variable within a site due to non-cohort enrollment
- Lower sensitivity
- · Season dependent, unless perennial rhinitis
- Less control over compliance
- Dependence on patient diaries

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Model 3 continued TRADITIONAL CLINICAL STUDY

Most Frequently Used for:

- Efficacy and safety
- Dose response
- Comparative studies

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Model 3 continued TRADITIONAL CLINICAL STUDY

<u>Bioequivalence Potential</u> HIGH - the best of all models

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Model 3 continued TRADITIONAL CLINICAL STUDY

Cost

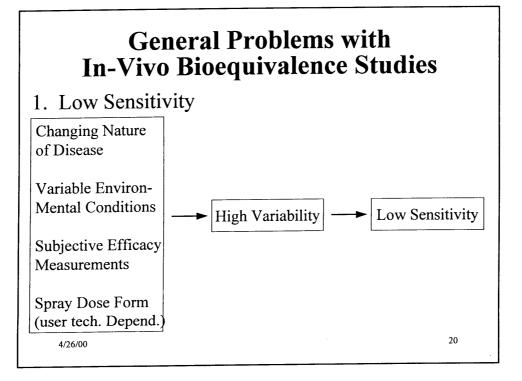
- 130 150 patients per treatment group
- Approx. \$1,200 grant per patient

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Improvements to Traditional Study Model

- Vehicle control rather than dose response
- No vehicle run-in period, in order to increase baseline severity and ability to discern differences in treatment groups
- Screening run-in for certain level of symptoms over days rather than only at randomization point.

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General Problems with In-Vivo Bioequivalence Studies continued

- 1. Limited or lack of dose response
- 2. Difficulty in blinding
- 3. Vehicle and placebo responses make it difficult to distinguish between treatments
- 3. Limited, gross, and non-standardized scales for efficacy measurements

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